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Institute Report No. 269

**Developmental Toxicity Potential of Hydroxyurea,
A Positive Control, in Rabbits**

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and
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**MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY**

May 1988

Toxicology Series: 145

**LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129**

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**Chemical Toxicity Potential of Hydroxyurea, a Positive
Control in Mice (Toxicology Series: 145) Coppes et al**

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF REPORT THIS DOCUMENT HAS BEEN APPROVED FOR PUBLIC RELEASE AND SALE: ITS DISTRIBUTION IS UNLIMITED		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
4. PERFORMING ORGANIZATION REPORT NUMBER(S) LAIR Institute Report No. 269					
6a. NAME OF PERFORMING ORGANIZATION Mammalian Toxicology Br. Division of Toxicology		6b. OFFICE SYMBOL (If applicable) SGRD-UL-TO-M		7a. NAME OF MONITORING ORGANIZATION	
6c. ADDRESS (City, State, and ZIP Code) Letterman Army Institute of Research Presidio of San Francisco, CA 94129-6800			7b. ADDRESS (City, State, and ZIP Code)		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION US Army Medical Research and Development Command		8b. OFFICE SYMBOL (If applicable)		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code) Ft. Detrick Frederick, MD 21701-5010		10. SOURCE OF FUNDING NUMBERS			
		PROGRAM ELEMENT NO. 62 720A	PROJECT NO. A835	TASK NO. AB	WORK UNIT ACCESSION NO DA303913
11. TITLE (Include Security Classification) Developmental Toxicity Potential of Hydroxyurea, a Positive Control, in Rabbits					
12. PERSONAL AUTHOR(S) Valerie G. Coppes, Charlotte L. Speckman, and Don W. Korte, Jr.					
13a. TYPE OF REPORT Institute		13b. TIME COVERED FROM 5/4/84 TO 26/7/84		14. DATE OF REPORT (Year, Month, Day) May 1988	
15. PAGE COUNT 88					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Developmental Toxicology, Teratology, Hydroxyurea Rabbit		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>The developmental toxicity potential of hydroxyurea was tested in pregnant New Zealand White rabbits. Hydroxyurea was administered by oral gavage on Days 6 through 18 of gestation. Dose levels tested were 0, 25, 50, 150, 200, 225, 300, and 450 mg/kg/day. Fetuses were delivered by cesarean section on Day 29 and weighed, examined externally, and processed in either Bouin's solution for visceral examination or alizarin red stain for skeletal examination. Pregnant females in the 225, 300, and 450 mg/kg/day groups had 100% resorptions. Hydroxyurea at dose levels of 50, 150, 200, 225, 300, and 450 mg/kg/day produced developmental toxic effects in New Zealand White rabbits. Malformations occurring in the 50, 150, and 200 mg/kg/day groups were underdevelopment of the heart atria, malformed tongue, situs inversus of the esophagus and stomach, cervical ribs, 14 pairs of ribs, and extra vertebrae.</p>					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED		
22a. NAME OF RESPONSIBLE INDIVIDUAL MAJ Don W. Korte, Jr.			22b. TELEPHONE (Include Area Code) 415 561-2963		22c. OFFICE SYMBOL SGRD-UL-T

ABSTRACT

The developmental toxicity potential of hydroxyurea was tested in pregnant New Zealand White rabbits. Hydroxyurea was administered by oral gavage on Days 6 through 18 of gestation. Dose levels tested were 0, 25, 50, 150, 200, 225, 300, and 450 mg/kg/day. Fetuses were delivered by cesarean section on Day 29 and weighed, examined externally, and processed in either Bouin's solution for visceral examination or alizarin red stain for skeletal examination. Pregnant females in the 225, 300, and 450 mg/kg/day groups had 100% resorptions. Hydroxyurea at dose levels of 50, 150, 200, 225, 300, and 450 mg/kg/day produced developmental toxic effects in New Zealand White rabbits. Malformations occurring in the 50, 150, and 200 mg/kg/day groups were underdevelopment of the heart atria, malformed tongue, *situs inversus* of the esophagus and stomach, cervical ribs, 14 pairs of ribs, and extra vertebrae

Key Words: Developmental Toxicity, Teratology, Hydroxyurea, Rabbit



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PREFACE

TYPE REPORT: Developmental Toxicity Study

TESTING FACILITY:

U.S. Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR:

U.S. Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

PROJECT: A835; Work Unit 180
Environmental Health Effects of Army Materials

STUDY NO.: 74021

STUDY DIRECTOR: Don W. Korte Jr, PhD, MAJ, MS

PRINCIPAL INVESTIGATOR: Valerie G. Coppes, BS

CO-PRINCIPAL INVESTIGATOR: Charlotte L. Speckman

REPORT AND DATA MANAGEMENT: A copy of the final report,
study protocol, addenda, retired
SOPs, and raw data will be
retained in the LAIR Archives.
Alizarin specimens will be
retained in the LAIR Pathology
Archives.

TEST SUBSTANCE: Hydroxyurea

INCLUSIVE STUDY DATES: 5 Apr 84 - 26 July 84


OBJECTIVE: The objective of this study was to demonstrate
the developmental toxicity of a positive control
compound, hydroxyurea, in the New Zealand White
rabbit in accordance with LAIR developmental
toxicity test standard operating procedures.

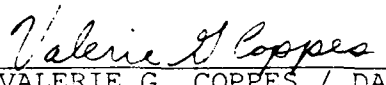
ACKNOWLEDGMENTS


SP5 Justo Rodriguez, BS, and Richard Katona assisted with the animal care.

**SIGNATURES OF PRINCIPAL SCIENTISTS
INVOLVED IN THE STUDY**

We, the undersigned, declare that Study 74021 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

 25 MAY 88
DON W. KORTE JR. PhD / DATE
MAJ, MS
Study Director

 25 May 88
VALERIE G. COPPES / DATE
DAC
Principal Investigator

 24 May 88
CHARLOTTE L. SPECKMAN / DATE
DAC
Co-Principal Investigator



DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-6800

REPLY TO
ATTENTION OF

SGRD-ULZ-QA

10 May 1988

MEMORANDUM FOR RECORD

SUBJECT: Quality Assurance Audit of non-GLP Study 74021

The raw data for non-GLP Study 74021 and the institute report entitled "Developmental Toxicity Potential of Hydroxyurea, a Positive Control, in Rabbits," Toxicology Series 145, was audited on 11 April 1988 and was found to be accurate.

Carolyn M. Lewis
CAROLYN M. LEWIS
Chief, Quality Assurance

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Developmental Toxicity Potential of Hydroxyurea, a Positive Control, in Rabbits -- Coppes et al

INTRODUCTION

The Toxicology Group, LAIR, has been tasked to perform toxicological evaluation of compounds to include developmental toxicity testing in two species, rat and rabbit. Developmental toxicity is the induction of adverse effects on the developing organism as a result of *in utero* exposure to an agent. The manifestations of developmental toxicity include death of the developing organism, structural abnormality (teratogenicity), altered growth, and functional deficiency. This report presents the results of a study to evaluate the developmental toxicity potential of a positive control, hydroxyurea, in rabbits.

Objective of the Study

The objective of this study was to demonstrate the developmental toxicity of a positive control compound, hydroxyurea, in the New Zealand White rabbit in accordance with LAIR developmental toxicity test standard operating procedures.

MATERIALS

Selection of the Positive Control

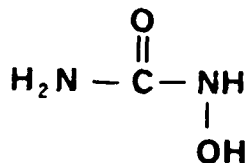
Hydroxyurea, a rapidly acting teratogen, is an inhibitor of DNA synthesis and a cytotoxic agent which selectively kills cells in the S-phase of the cell cycle (1).

Positive Control Substance

Chemical Name: Hydroxyurea

Chemical Abstract Service Registry No.: 127-07-1

Molecular Structure: $\text{CH}_4 \text{ N}_2 \text{ O}_2$



Molecular Weight: 76.06

Source: Sigma Chemical Company
P.O. Box 14508
St. Louis, MO 63178

Additional information about the positive control appears in Appendix A.

Vehicle

The vehicle for hydroxyurea was sterile water for injection obtained from Cutter Laboratories, Inc, Emeryville, CA, and Abbott Laboratories, North Chicago, IL. Expiration dates were February 1985 and March 1986.

Animal Data

Thirty-two female and eight male New Zealand White rabbits were obtained from Elkhorn Rabbitry, Watsonville, CA. They were identified individually by ear tattoo numbers 84F237 through 84F268 for the females and 84F269 through 84F276 for the males. The weights of the females ranged from 3.28 to 4.47 kg, and the weights of the males ranged from 3.67 to 4.62 kg when released from quarantine. Additional animal data appear in Appendix B.

The rabbit has proven to be a sensitive test system for teratology studies (2). Historic data on malformations and variants in New Zealand White rabbits are well documented (3, 4).

Husbandry

Upon arrival at LAIR rabbits were quarantined for 14 days. After release from quarantine rabbits were housed individually in stainless steel wire mesh cages in racks equipped with automatically flushing dump tanks. Bedding was not provided. Rabbits were fed Purina Rabbit Chow 5315

(Ralston Purina Company, St. Louis, MO). Nonpregnant rabbits were fed approximately 120 grams of chow per day, and pregnant rabbits were fed approximately 180 grams per day from 18 Apr 84 until 10 Jun 84. The feed was increased to approximately 180 grams per day for nonpregnant animals and approximately 240 grams per day for pregnant animals on 11 Jun 84. Water was provided by automatic water dispensers. The animal room temperature was maintained in a range between 17°C and 22°C with a relative humidity range between 42 and 76% with occasional spikes up to 98% during room cleaning. The photoperiod was 12 hours of light per day.

METHODS

Methods used are described in detail in LAIR "Teratology Testing Procedure" OP-STX-40 (5) and were in accordance with Environmental Protection Agency and Food and Drug Administration guidelines for developmental health effects (6,7).

Acclimation

After release from quarantine, each female was predosed with water several times during a six day acclimation period. Animals were observed daily for signs of illness.

Group Assignment

Females were assigned to test groups according to OP-1SG-21 "Animal Randomization Procedure" on the Data General ECLIPSE C/330 computer (8). Sequences of numbers corresponding to the number of dose groups were generated. As females were bred, they were assigned to one of the dose groups.

Dosage Levels/Administration

The dosage levels of hydroxyurea tested were 0, 25, 50, 150, 200, 225, 300 and 450 mg/kg/day. Bred females were dosed daily from Day 6 through Day 18 of gestation. Day 0 was the day of breeding. The dosage was calculated on the Day 6 body weight and administered in a volume of 2 ml/kg body weight. Vehicle control animals received sterile water at a volume of 2 ml/kg body weight. Animals were dosed by oral intubation using a 10-cc syringe equipped with a 13-cm length of polyethylene tubing, inner diameter 1.67 mm, outer diameter 2.42 mm (Clay Adams, Parsippany, NJ). Bred females were dosed from 30 Apr 84 through 15 Jul 84.

Compound Preparation

Dosing solutions were prepared by mixing hydroxyurea in an appropriate volume of sterile water for injection. The preparations were heated slightly to attain complete dissolution and refrigerated. Before dosing the animals, the vials were warmed slightly to redissolve crystallized hydroxyurea.

Breeding

Each female was bred randomly to one or two males. Mating was confirmed by observation of the pair mating. The day of mating was designated as Day 0 of gestation. Females were bred from 24 Apr 84 through 27 Jun 84.

Cesarean Section Procedure

Dams were weighed and euthanized with CO₂ on Day 29 of gestation. All females were examined, and nonpregnant ones were removed from the study. Gravid uteri were examined for number of implantation sites, resorptions, and live and dead fetuses. The uterus and ovaries were removed and the corpora lutea counted. The dams were examined for gross visceral signs of toxicity and reweighed. Each fetus was weighed, measured crown-to-rump, and examined externally. Fetuses were assigned alternately to either skeletal or visceral examination groups.

Fetuses assigned for skeletal examination were placed in 70% ethanol and processed by the alizarin red S staining technique of Crary (9). After processing, the specimens were placed in glycerol with a few crystals of thymol to inhibit bacterial and mold growth. Fetuses assigned for visceral examination were placed in Bouin's solution. The body walls were pierced to allow penetration of the fixing solution.

Observations and Records

Bred females were weighed on Days 0, 6, 12, 18, 24, and 29 of gestation. Females were observed daily from Day 0 through Day 29 for clinical signs of toxicity, abortion, or premature delivery. Date, time, and amount of dosing solution administered were recorded during the daily dosing on Days 6 through 18. At cesarean section, body weight, uterine data, and results from gross examination of the dam were recorded. The dams were reweighed after removal of the gravid uterus to obtain the Corrected Day 29 weight.

Fetal weight, crown-to-rump measurement, and external examination findings from live fetuses were recorded. Bouin's fetuses were examined under low magnification by the modified Wilson freehand razor blade sectioning technique (10). The skeletons stained by alizarin were examined under low magnification on a light box for degree of ossification, malformations, and alignment. The sternebrae, ribs, vertebrae, metacarpals, and metatarsals were counted.

Schedule of Study Events

The historical listing of study events is given in Appendix C.

Statistical Analysis

Means and standard deviations were performed on maternal weights, uterine, and litter data.

Deviations from Original Protocol

Females were bred by two males rather than one to increase pregnancy rate. The breeding period was extended from two weeks to two months, until all females were bred. The first litters were examined to determine whether adjustments in the dose levels were appropriate for the remaining females. The original protocol specified five dose groups: 0, 50, 150, 300, and 450 mg/kg/day hydroxyurea. On study Day 16 the first female assigned to the 450 mg/kg/day group died. Because the teratology testing procedure recommends less than 10% maternal deaths in the high dose group, it was determined that 450 mg/kg/day hydroxyurea administered on 13 consecutive days was too high (5). Two other females also assigned to this group were dosed with 450 mg/kg/day hydroxyurea on Days 6 through 10; then because of the death of the first female, the dosage was lowered on Day 11 to 300 mg/kg/day for the remainder of the dosing period. A lower dose group, 25 mg/kg/day hydroxyurea, was included in the study. A fourth female assigned to the 450 mg/kg/day dose group, but not yet dosed, was transferred to the 25 mg/kg/day dose group. After cesarean sectioning of the earliest bred animals, it was determined that intermediate doses between 150 mg/kg/day and 300 mg/kg/day were needed to demonstrate a dose-response relationship. Two new dose groups, 200 mg/kg/day and 225 mg/kg/day, were included in the study.

These adjustments to the original dose levels were necessary to prevent maternal deaths, to demonstrate a dose-related developmentally toxic effect, and to estimate the no-observed-effect level.

Raw Data and Final Report Storage

A copy of the final report, study protocol, addenda, raw data, and SOPs will be retained in the LAIR Archives. Alizarin specimens will be retained in LAIR Pathology Archives.

RESULTS

Maternal Data

The number of bred animals assigned to each group, number of animals that died, number of animals that were pregnant, and number of animals with live litters are presented in Table 1. There was no difference in percent of pregnant animals with live litters in the 0, 25, 50, 150, and 200 mg/kg/day hydroxyurea dose groups. The pregnant females in the 225, 300, and 450 mg/kg/day dose groups had no live litters.

One maternal death occurred on study Day 16 in the 450 mg/kg/day dose group. Necropsy findings reported the death was most likely caused by bacteremia/septicemia brought about by necrosis of small intestine mucosa. The necrosis may have been caused or aggravated by the test compound, hydroxyurea.

Individual maternal weights and weight changes are listed in Appendix D, and the group means are presented in Table 2. Slight weight loss occurred in most dose groups (not dose-related) during the study period (Corrected Day 29 weight - Day 0 weight). During the treatment period (Day 18 weight - Day 6 weight), weight gain occurred in all dose groups except that the animals assigned to the 450 mg/kg/day group, which had been dosed with 450 mg/kg/day from Days 6 through 10 and 300 mg/kg/day from Days 11 through 18, lost weight.

Individual maternal clinical signs and necropsy findings are listed in Appendix E. Clinical signs per group during pretreatment (Day 0 through Day 5), treatment (Day 6 through Day 18), posttreatment (Day 19 through Day 28), and necropsy findings at cesarean section (Day 29) are found in Tables 3a, b, c, and d, respectively. One female, 84F264 in the control group, aborted on Day 22 and was euthanized on Day 29. Off

feed (animal did not eat approximately 1/4 or more of its daily feed ration) was the most frequent clinical sign during the pretreatment, treatment, and posttreatment periods and was not dose-related. Clinical signs that occurred more frequently in the 300 or 450 mg/kg/day dose groups during treatment and posttreatment were salivation; inactivity; alopecia; pallor of lips, nose, and gums; and death. At cesarean section, dark spots on ovaries was the only dose-related sign of maternal toxicity.

Cesarean/Fetal Data

The individual number of implantations, resorptions, percent resorptions, and number and percent of live and dead fetuses are listed in Appendix F. The summary by group is presented in Table 4. The 225, 300, and 450 mg/kg/day dose groups had lower implantation efficiencies and higher resorption rates than the control group. Hydroxyurea produced 100% resorptions in the three high dose groups and a dose-dependent increase in percentage of dead fetuses in the 50, 150, and 200 mg/kg/day groups. The individual fetal sex, weight, and crown-to-rump length are given in Appendix G. The group means are presented in Table 5. The fetuses in the 200 mg/kg/day group were lighter in weight and shorter in length than the controls or lower hydroxyurea groups.

Individual external examination findings are presented in Appendix H. A summary by dose group is in Table 6. External malformations and variants occurred in the 150 and 200 mg/kg/day dose groups.

Individual visceral examination findings are presented in Appendix I. A summary by dose group is in Table 7. Visceral variants were dose-related, ranging between 20% in the control group and 57% in the 200 mg/kg/day group, with the exception of 80% occurring in the 25 mg/kg/day dose group. Since the 80% represented only one litter, this is considered an aberration rather than dose-related. Visceral malformations occurring in the 50, 150, and 200 mg/kg/day dose groups were marked underdevelopment of heart atria, situs inversus of esophagus and stomach, ectopic kidney, and malformed tongue.

Individual skeletal examination findings are presented in Appendix J. A summary by dose group is provided in Table 8. Skeletal variants occurred in high frequency in all groups. Many fetuses had 13 pairs of ribs or a unilateral 13th rib. Split, unilaterally ossified, fused, scrambled, or diagonally shaped sternbrae occurred frequently in the 150 and 200 mg/kg/day dose groups. There were no differences in

the number of sternebrae, coccygeal vertebrae, metacarpals, metatarsals, and phalanges ossified between groups. Skeletal malformations were dose-related and were found in the 150 and 200 mg/kg/day dose groups. Twenty or 21 thoracic and lumbar vertebrae (19 is the normal number) occurred in 74% of the 150 mg/kg/day dose group and in 62% of the 200 mg/kg/day dose group fetuses. Rudimentary cervical rib occurred in 62% of the 200 mg/kg/day dose group fetuses compared to 4% (one fetus) in the control group. Eight cervical vertebrae (seven is the normal number) occurred in 26% of the 150 mg/kg/day fetuses and in 100% of the 200 mg/kg/day fetuses. Misaligned and fused coccygeal vertebral arches occurred in two fetuses in the 200 mg/kg/day dose group.

The individual incidence of external, visceral, and skeletal variations and malformations is found in Appendix K. A summary by dose group of the effect of hydroxyurea on the incidence of fetal malformations and variations is presented in Table 9. Variants occurred in all dose groups. Malformations were dose-related, increasing in frequency with increasing dose levels of hydroxyurea.

Table 1
Effect of Hydroxyurea on Survival and Pregnancy

	Hydroxyurea (mg/kg/day)							
	0	25	50	150	200	225	300	450
Bred females	7	1	4	4	4	4	4	3
Number that died	0	0	0	0	0	0	0	1
Percent that died	0	0	0	0	0	0	0	33
Number surviving to Day 29	7	1	4	4	4	4	4	2*
Gravid	6	1	3	4	2	1	4	2
Percent gravid	86	100	75	100	50	25	100	100
With live litters	5	1	3	4	2	0	0	0
Percent with live litters	83	100	100	100	100	0	0	0

*Dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

Table 2
Effect of Hydroxyurea on Maternal Body Weights and Weight Changes*

Day	Hydroxyurea (mg/kg/day)							
	0	25	50	150	200	225	300	450†
0	3.98 ± .50	4.18	4.00 ± .26	3.69 ± .25	3.80 ± .22	3.91	3.83 ± .08	3.91 ± .30
6	4.09 ± .38	4.08	4.16 ± .20	3.79 ± .32	3.95 ± .28	3.99	3.83 ± .17	4.02 ± .31
12	4.18 ± .42	4.23	4.16 ± .22	3.88 ± .29	4.07 ± .29	4.06	3.84 ± .12	3.89 ± .28
18	4.20 ± .57	4.24	4.26 ± .19	4.00 ± .27	4.20 ± .33	4.20	3.78 ± .12	3.59 ± .37
24	4.26 ± .57	4.27	4.37 ± .24	4.08 ± .27	4.17 ± .21	4.16	3.76 ± .11	3.77 ± .43
Gravid								
29	4.35 ± .50	4.40	4.42 ± .28	4.16 ± .32	4.31 ± .21	4.18	3.76 ± .11	3.67 ± .35
Corrected								
29	3.92 ± .38	3.83	3.87 ± .28	3.62 ± .28	3.86 ± .19	4.14	3.73 ± .09	3.65 ± .35
Weight Change								
Study Periods								
-0.07 ± .19	-0.35	-0.13 ± .05	-0.07 ± .10	0.06 ± .03	0.23	-0.09 ± .03	-0.17 ± .01	
Treatment Period‡								
0.11 ± .32	0.16	0.10 ± .05	0.21 ± .22	0.25 ± .04	0.21	0.15 ± .50	-0.34 ± 0	

*Mean ± S.D. in kg for pregnant females.

†One animal in this group died on Day 16. The remaining 2 animals in this group were dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

‡Group mean of [Corrected Day 29 weight - Day 0 weight].

«Group mean of [Day 18 weight - Day 6 weight].

Table 3a

Maternal Clinical Signs* - Pretreatment (Days 0-5)

	Hydroxyurea (mg/kg/day)									
	0	25	50	150	200	225	300	450		
Number of animals observed	6	1	3	4	2	1	4	3		
Number with signs	2	0	0	0	2	1	1	0		
Abscess, dewclaws	1									
Off feed	1				1	1	1			
Brown material, perianal					1					
Yellow dried mucus around eyes					1					
Yellow-stained nose, forepaws					1					

*Pregnant females.

Table 3b

Maternal Clinical Signs* - Treatment (Days 6-18)

	Hydroxyurea (mg/kg/day)									
	0	25	50	150	200	225	300	450		
Number of animals observed	6	1	3	4	2	1	4	3†		
Number with signs	6	1	3	1	2	1	4	3†		
Abscess, dewclaws	1									
Off feed	5		3	1	2	1	4	3†		
Yellow-stained nose/mouth	3	1	1	1			1	1\$		
Yellow-stained paws			1							
Misdose	1		1							
Salivation										
Diarrhea							1	2\$		
Brown-stained perianal	1							1		
Soft feces	1					1				
Yellow-stained perianal							1			
Sound production					1					
Convulsion, tonic										
Tremors										
Depressed corneal reflex										
Dosing discontinued										
Inactive										
Pallor, lips/gums	1									
Death							1			

*Pregnant females.

Two animals were dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

One animal dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

Table 3c

Maternal Clinical Signs* - Posttreatment (Days 19-28)

	Hydroxyurea (mg/kg/day)									
	0	25	50	150	200	225	300	450†		
Number of animals observed	6	1	3	4	2	1	4	2		
Number with signs	5	0	3	2	2	1	4	2		
Abscess, dewclaws	1									
Off feed	3		1	1	2	1	4	1		
Yellow stained nose/mouth	4		1	2	1					
Nasal discharge, clear							1			
Nasal discharge, mucous	1									
Yellow-stained forepaws		.	2	:						
Rapid breathing	1									
Diarrhea					1					
Soft feces	1			:	1	1	1			
Aborted	1									
Bloody vaginal discharge										
Pallor, lips/nose/gums										
Hair pulling to make nest							2			
Alopecia, head						1				
Alopecia, paws										
Alopecia, hind legs										
Hypertonia										

*Pregnant females.

†Dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

Table 3d

Maternal Necropsy Findings* - At Cesarean Section (Day 29)

	Hydroxyurea (mg/kg/day)							
	0	25	50	150	200	225	300	450†
Number of animals observed	6	1	3	4	2	1	4	2
Number with signs	2	0	1	4	2	1	4	2
Small ovaries							1	
Dark spots on ovaries	1		1	2	2	1	4	2
Cysts on ovaries				1	1			
Cysts on fallopian tubes	2			1		1	1	
Fluid in vagina						1		
Corpora lutea, small, hard, red						1		
Liver torsion								1
Pale areas on liver				1				
Lungs pale, dark red spots					1			
Cysts on spleen				1				
Gall bladder enlarged, soft				1				
Gall bladder, off-white	1							

*Pregnant females.

†Dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

Table 4
Effect of Hydroxyurea on Mean Gestational Data

	Hydroxyurea (mg/kg/day)							
	0	25	50	150	200	225	300	450*
Number of corpora lutea	10.6	14	10.7	12.2	10.5	10	12.2	15.0
Number of implantations	9.0	12	9.7	10.2	9.0	4	7.5	10.0
Percent implantation efficiency†	83.2	86	90.7	83.2	86.0	40	60.7	67.0
Number of resorptions	0.2	1	0.3	0.8	0.5	4	7.5	10.0
Percent resorptions‡	4.0	8	3.7	7.4	5.5	100	100.0	100.0
Number of fetuses								
Dead	0.2	0	0.7	0.8	1.0	0	0	0
Percent dead»	2.0	0	6.0	6.9	11.0	0	0	0
Live fetuses	8.6	11	9.7	8.8	7.5	0	0	0
Percent live=	94.0	92	90.3	85.7	83.5	0	0	0

*Dosed with 450 mg/kg/day hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

†Group mean of [implantations per litter/corpora lutea per litter] X 100

‡Group mean of [resorptions per litter/implantations per litter] X 100

»Group mean of [dead fetuses per litter/implantations per litter] X 100

=Group mean of [live fetuses per litter/implantations per litter] X 100

Table 5
Effect of Hydroxyurea on Litter Size, Sex, Weight, and Length*

	Hydroxyurea (mg/kg/day)				
	0	25	50	150	200
Live fetuses	8.6 ±	11.0	8.7 ±	8.8 ±	7.5 ±
Males	5.4 ±	6.0	3.0 ±	4.2 ±	4.5 ±
Females	3.2 ±	5.0	5.7 ±	4.5 ±	3.0 ±
Percent males	56.8 ±	54.6	34.3 ±	46.5 ±	59.8 ±
Body weight (g)	38.9 ±	35.3	40.9 ±	36.8 ±	34.4 ±
Males	38.9 ±	35.4	40.4 ±	36.2 ±	33.9 ±
Females	38.5 ±	35.2	41.2 ±	36.8 ±	34.9 ±
Crown-rump length (mm)	94.3 ±	93.1	97.2 ±	94.6 ±	92.0 ±
Males	95.1 ±	93.0	97.1 ±	93.5 ±	91.5 ±
Females	93.9 ±	93.2	96.8 ±	95.2 ±	92.3 ±

*Mean ± S.D. of litter means

Table 6
External Malformations and Variations in Fetuses of Hydroxyurea-treated Rabbits

	Hydroxyurea (mg/kg/day)				
	0	25	50	150	200
Fetuses/litters	43/5	11/1	26/3	35/4	15/2
Variants					
Body dark red					1/1
Malformations					
Forepaw hyperflexed				1/1	2/1
Tail Curly					1/1
Tongue malformed					

A single fetus may have more than one abnormality and, therefore, would occur more than once in this table.

Table 7
Visceral Malformations and Variations in Fetuses of Hydroxyurea-treated Rabbits

	Hydroxyurea (mg/kg/day)				
	0	25	50	150	200
Fetuses/litters	20/5	5/1	12/3	16/4	7/2
Variants					
Nasal concha underdeveloped	1/1			3/2	3/2
Cerebrum underdeveloped	1/1				
Lateral ventricle dilated	1/1	1/1	1/1	1/1	
Arachnoid space dilated		1/1		1/1	
Foramen magnum dilated		1/1			
Heart ventricle enlarged					1/1
Heart atria small		1/1		2/1	
Gall bladder small		1/1			
Kidney small					
Kidney lobular	1/1		1/1		
Renal pelvis dilated			1/1	1/1	1/1
Ovary short/thickened			1/1	1/1	
Malformations					
Heart atria underdeveloped			1/1	1/1	1/1
Renal malformation					
Esophageal atresia/intestine				1/1	
Stomach/intestine malformation			1/1		2/2
Kidney atrophy					

A single fetus may have more than one abnormality and, therefore, would occur more than once in this table.

Table 8
Skeletal Malformations and Variations in Fetuses of Hydroxyurea-treated Rabbits

	Hydroxyurea (mg/kg/day)				
	0	25	50	150	200
Fetuses/Litters	23/5	6/1	14/3	19/4	8/2
Variants					
Horns of hyoid not ossified					1/1
Frontal/parietal suture jagged				1/1	
Ribs:					
13 pairs	18/5	5/1	14/3		3/2
Unilateral rudimentary 13th	4/3				
Short 13th	3/3	1/1			
Short 1st				2/2	
Scapula spine crooked	1/1			1/1	
Sternebrae:					
Split/unilateral ossification	2/1			4/3	1/1
Fused				2/2	
Scrambled				2/1	
Diagonal shape					1/1
Vertebral centrum split/malrotated					1/1
Sacral vertebral arch wide					1/1
Radius and ulna small				1/1	
Pubis incomplete ossification				1/1	
					1/1
					1/1

A single fetus may have more than one abnormality and, therefore, would occur more than once in this table.

Table 8 (Concluded)
Skeletal Malformations and Variations in Fetuses of Hydroxyurea-treated Rabbits

		Hydroxyurea (mg/kg/day)				
		0	25	50	150	200
Fetuses/Litters		23/5	6/1	14/3	19/4	8/2
Malformations						
Ribs:		1/1				5/2
Rudimentary cervical					8/2	
14 pairs					1/1	
Unilateral 14th						
Vertebrae:						
8 cervical					5/1	8/2
20 thoracic + lumbar					13/4	5/2
21 thoracic + lumbar					1/1	
Scoliosis						1/1
Coccygeal vertebrae misaligned/fused						2/1

A single fetus may have more than one abnormality and, therefore, would occur more than once in this table.

Table 9
Effect of Hydroxyurea on the Incidence of Fetal Malformations and Variations

	Hydroxyurea (mg/kg/day)				
	0	25	50	150	200
Number fetuses/litters	43/5	11/1	26/3	35/4	15/2
Any (External/Visceral/Skeletal) Malformations	1/1	0/0	2/1	18/4	11/2
Variations	26/5	9/1	17/3	21/4	9/2
External examination Malformations	0/0	0/0	0/0	1/1	3/2
Variations	0/0	0/0	0/0	0/0	1/1
Visceral examination Number fetuses/litters	20/5	5/1	12/3	16/4	7/2
Malformations	0/0	0/0	2/1	2/2	3/2
Variations	4/3	4/1	3/3	6/2	4/2
Skeletal examination Number fetuses/litters	23/5	6/1	14/3	19/4	8/2
Malformations	1/1	0/0	0/0	16/4	8/2
Variations	22/5	5/1	14/3	15/4	4/2

DISCUSSION

Developmental toxicity is the induction of adverse effects on the developing organism as a result of *in utero* exposure to an agent. The manifestations of developmental toxicity include death of the developing organism, structural abnormality (teratogenicity), altered growth, and functional deficiency. The no-observed-effect level is the maximum concentration in a test which produces no observed adverse effects (6).

In this study, death of the developing organism was dose-related. The 225, 300, and 450 mg/kg/day dose groups had 100% resorptions (no live or dead fetuses), and the percent dead fetuses ranged from 2% in the control to 11% in the 200 mg/kg/day dose groups. External, visceral, and skeletal malformations were dose-related and occurred in the 50, 150, and 200 mg/kg/day dose groups. There were no malformations in the 25 mg/kg/day dose group. The presence of supernumerary 13th ribs at the thoracolumbar border is one of the most common variants in rabbits. The presence of a cervical rib is quite common in mice, but is a relatively rare anomaly in rabbits (4). The spontaneous occurrence of supernumerary lumbar ribs is highly variable and determined by both genetic and extragenetic factors which influence the differentiation and growth of rib precursors at a specific stage of embryogenesis. The presence of extra vertebrae is much less common. Chemical agents, maternal stress, and embryo-toxicity attributed to maternal treatment have been associated with extra ribs (11). In this study, having 13 pairs of ribs, rather than the normal 12, was considered a variant, but 14 pairs of ribs, cervical ribs, and eight cervical or more than 19 thoracic + lumbar vertebrae were considered malformations. With the exception of one control fetus with a cervical rib, these malformations occurred only in the 150 and 200 mg/kg/day dose groups. Morphological changes such as these are interpreted with caution, and the test substance is considered a developmental hazard only when morphological changes occur in conjunction with other observations such as increased fetal loss (3). While increased numbers of vertebrae, 14 pairs of ribs, *situs inversus* of esophagus and stomach, and malformed tongue generally are not incompatible with life, they are permanent structural deviations from normal. Severely underdeveloped heart atria, which occurred in the 50 and 150 mg/kg/day dose groups, may be incompatible with or severely detrimental to normal postnatal survival. One fetus in the 150 mg/kg/day dose group had a hyperflexed forepaw. Since skeletal examination of this fetus revealed no abnormalities, the flexure may have disappeared with postnatal exercise and was not considered a skeletal malformation.

Although the dose level and time of administration were different, some of the findings in this study, such as high resorption rates, ectopic kidneys, stunted tails, and abnormal vertebrae, have also been reported in New Zealand White rabbits injected s.c. on Day 12 of gestation with 750 mg/kg hydroxyurea (12). The data support a dose-response increase in developmental toxicity with the positive control, hydroxyurea.

CONCLUSION

When given in oral doses of 50, 150, 200, 225, 300, and 450 mg/kg/day from Days 6 through 18 of gestation, the positive control substance, hydroxyurea, produced developmental toxic effects in New Zealand White rabbits. The LAIR developmental toxicity testing procedure for New Zealand White rabbits is a valid model for testing substances for developmental toxicity.

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Appendix A Chemical Data
Appendix B Animal Data
Appendix C Schedule of Study Events
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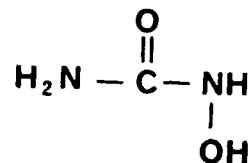
APPENDICES

Chemical Data

Chemical name: Hydroxyurea; Hydroxycarbamide; Hydrea;
Litalir

Chemical Abstract Service Registry No.: 127-07-1

Structural formula:



Molecular formula: $\text{CH}_4\text{N}_2\text{O}_2$

Molecular weight: 76.06

Source: Sigma Chemical Company
P.O. Box 14508
St. Louis, MO 63178

<u>Lot No.</u>	<u>Date of dosing solution preparation</u>
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73F-0643	30 Apr 84, 4 May 84
73F-0375	10 May 84, 21 May 84, 14 Jun 84
103F-0140	25 Jun 84, 28 Jun 84, 7 Jul 84

Solubility: Freely soluble in water, hot alcohol*.

* Windholz M, ed. The Merck Index. Tenth Edition.
Rahway, NJ: Merck and Co., 1983:4772.

Animal Data

Species: Rabbit

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA

Sex: 32 Females and 8 Males

Age:

Male: Age unknown, adult, proven breeders.

Female: Approximately 5 months, nulliparous.

Condition of animals at start of study: Normal

Body weight range of females at dosing: 3.39 - 4.61 kg

Schedule of Study Events

Date	Event
17 Feb 84	Date protocol approved.
5 Apr 84	Rabbits arrived at LAIR.
18 Apr 84	Rabbits released from quarantine.
19-23 Apr 84	Rabbits pre-dosed with water.
23 Apr-27 Jun 84	Several female rabbits bred per day.
30 Apr-15 Jul 84	Bred females dosed.
23 May-26 Jul 84	Cesarean sections.

Individual Maternal Body Weights* - Control Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 18-6\$
84F238	3.63	3.81	3.91	4.00	4.07	4.25	3.74	0.11 0.19
(84F243)	(4.13)	(3.96)	(3.95)	(4.01)	(4.13)	(4.14)	(4.12)	(-0.01) (0.05)
84F246	3.67	3.86	3.90	4.03	4.27	4.36	3.78	0.11 0.17
84F251	4.66	4.57	4.73	4.86	4.86	4.76	4.48	-0.18 0.29
84F258	3.59	3.81	3.84	4.11	4.09	4.17	3.68	0.09 0.30
84F260	4.51	4.60	4.69	4.85	4.90	4.99	4.32	-0.19 0.25
84F264	3.84	3.91	4.00	3.37	3.38	3.55	3.53	-0.31 -0.54

*Weights in kg. Parentheses indicate that animal was not pregnant at cesarean section.
 †Study period (Day 29 Corrected - Day 0).
 \$Treatment period (Day 18 - Day 6).

Individual Maternal Body Weights* - 25 gm/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation					Weight Change
	0	6	12	18	24	
					Gravid 29	Corrected 29
84F266	4.18	4.08	4.23	4.24	4.37	4.40
						3.83
						-0.35
						0.16

*Weights in kg.

†Study period (Day 29 Corrected - Day 0).

§Treatment period (Day 18 - Day 6).

Individual Maternal Body Weights* - 50 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 11-65
84F244	3.73	4.00	3.97	4.07	4.13	4.11	3.56	-0.18 1.07
(84F249)	(3.81)	(3.80)	(3.87)	(3.93)	(4.05)	(3.99)	(3.96)	(0.15) (0.13)
84F253	4.02	4.10	4.11«	4.26	4.38	4.49	3.93	-0.09 1.16
84F261	4.25	4.38	4.40	4.45	4.60	4.66	4.12	-0.13 1.17

*Weights in kg. Parentheses indicate that animal was not pregnant at cesarean section.
†Study period (Day 29 Corrected - Day 0).

§Treatment period (Day 18 - Day 6).

«Weighed on Day 12.

Individual Maternal Body Weights* - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 18-6S
84F255	3.58	3.83	3.79	3.94	4.01	4.24	3.65	0.07 0.11
84F259	3.56	3.39	3.75	3.90	3.97	3.96	3.41	-0.15 0.51
84F263	4.06	4.16	4.31	4.40	4.47	4.57	4.00	-0.06 0.24
84F267	3.56	3.77	3.67	3.77	3.85	3.85	3.42	-0.14 0

*Weights in kg.

†Study period (Day 29 Corrected - Day 0).

‡Treatment period (Day 18 - Day 6).

Individual Maternal Body Weights* - 200 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 18-6\$
(84F245)	(3.84)	(4.16)	(4.16)	(4.11)	(4.22)	(4.24)	(4.23)	(0.39) (0.05)
84F250	3.64	3.75	3.86«	3.97	4.02	4.16	3.72	0.08 0.22
(84F252)	(4.09)	(4.42)	(4.42)	(4.34)	(4.29)	(4.39)	(4.36)	(0.27) (-0.08)
84F254	3.95	4.15	4.27	4.43	4.32	4.45	3.99	0.04 0.28

*Weights in kg. Parentheses indicate that animals were not pregnant at cesarean section.

†Study period (Day 29 Corrected - Day 0).

\$Treatment period (Day 18 - Day 6).

«Weighed on Day 11.

Individual Maternal Body Weights* - 225 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 18-6\$
(84F240)	(3.63)	(3.98)	(3.97)	(3.89)	(3.99)	(4.11)	(4.09)	(0.45) (-0.09)
(84F241)	(3.95)	(3.96)	(4.06)	(4.11)	(4.16)	(4.16)	(4.14)	(0.18) (0.15)
84F256	3.91	3.99	4.06	4.20	4.16	4.18	4.14	0.23 0.21
(84F265)	(4.27)	(4.61)	(4.54)	(4.64)	(4.57)	(4.63)	(4.61)	(0.34) (0.03)

*Weights in kg. Parentheses indicate that animals were not pregnant at cesarean section.

†Study period (Day 29 Corrected - Day 0).

\$Treatment period (Day 18 - Day 6).

Individual Maternal Body Weights* - 300 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation						Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29	29C-0† 18-6\$
84F239	3.75	3.93	3.77	3.87	3.79	3.68	3.68	-0.07 -0.06
84F248	3.92	4.02«	3.92	3.87	3.88	3.92	3.85	-0.06 -0.15
84F262	3.77	3.71	3.71	3.61	3.62	3.68	3.66	-0.11 -0.10
84F268	3.86	3.67	3.95	3.76	3.76	3.76	3.74	-0.12 0.90

*Weights in kg.

†Study period (Day 29 Corrected - Day 0).

\$Treatment period (Day 18 - Day 6).

«Weighed on Day 13.

Individual Maternal Body Weights* - 450 mg/kg/day Hydroxyurea Animals

Maternal ID	Day of Gestation					Weight Change	
	0	6	12	18	24	Gravid 29	Corrected 29
84F242«	3.57	3.66	3.56	3.32	3.46	3.42	3.40
84F247	4.11	4.21	4.08≈				
84F257«	4.06	4.19	4.02	3.85	4.07	3.91	3.89

*Weights in kg.

†Study period (Day 29 Corrected - Day 0).

‡Treatment period (Day 18 - Day 6).

«Dosed with 450 mg/kg/day from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18

≈Weighed on Day 13. Animal died Day 16.

Individual Maternal Clinical Signs - Control Animals

Maternal ID	Study Day (s)	Date(s)	Signs
84F238	0 - 28	27 Jun - 26 Jul 84	Abscess both dewclaws, cleaned daily with hydrogen peroxide and Betadine.
	7 - 22	4 - 19 Jul 84	Yellow stained nose
	27 - 29	24 - 26 Jul 84	Yellow stained nose
	19 - 21	16 - 18 Jul 84	Off feed
	20 - 22	17 - 19 Jul 84	Rapid breathing
	27	24 Jul 84	Rapid breathing
84F246	29	26 Jul 84	At cesarean section, cysts on fallopian tubes.
	0 - 4	25 - 29 Jun 84	Off feed
	7 - 8	2 - 3 Jul 84	Off feed
	14 - 17	9 - 12 Jul 84	Off feed
	21 - 25	16 - 20 Jul 84	Off feed
	28	23 Jul 84	Off feed
84F251	14	14 May 84	Off feed
84F258	7	10 May 84	Possible misdose, white liquid from nose after dosing.
	18	21 May 84	Off feed
	21 - 22	24 - 25 May 84	Yellow stained nose, mouth

Individual Maternal Clinical Signs - Control Animals (Concluded)

Maternal ID	Study Day(s)	Date(s)	Signs
84F260	6	30 Apr 84	Off feed
	14	8 May 84	Off feed
	17 - 18	11 May 84	Yellow stained nose
	20	14 May 84	Yellow stained nose
	23	17 May 84	Yellow stained nose
	27	21 May 84	Soft feces
	28	22 May 84	Yellow stained nose
84F264	11	21 May 84	Soft feces
	11 - 13	21 - 23 May 84	Off feed
	12 - 15	22 - 25 May 84	Brown stained perianal
	16	23 May 84	Yellow stained mouth
	14	24 May 84	Inactive
	19 - 22	25 May - 1 Jun 84	Off feed
	16 - 17	26 - 27 May 84	Soft feces
	21	31 May 84	Yellow stained nose; nasal discharge, mucus
	22	1 Jun 84	Aborted, 4 fetuses (1x2 cm) found under cage, bloody vaginal discharge
			Nasal discharge, mucus
	23 - 24	2 - 3 Jun 84	Yellow stained nose
	25	2 Jun 84	Off feed
	25	4 Jun 84	At cesarean section, right ovary had a dark spot; cysts on fallopian tubes; gall bladder, off-white
	29	5 Jun 84	

Individual Maternal Clinical Signs - 25 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day (s)	Date (s)	Signs
84F266	10	17 May 84	Yellow stained nose

Individual Maternal Clinical Signs - 50 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day(s)	Date(s)	Signs
84F244	18	21 May 84	Off feed
	20 - 21	23 May 84	Yellow stained forepaws
	29	1 Jun 84	At cesarean section, dark spots on ovaries
84F253	6	30 Apr 84	Off feed
	9	3 May 84	Misdose, approximately 1/2 dosing solution spit out
	21 - 22	15 - 16 May 84	Off feed
84F261	27	21 May 84	Off feed
	7 - 8	16 - 17 May 84	Yellow stained nose
	13	22 May 84	Off feed
	13 - 14	22 - 23 May 84	Yellow stained nose
	15 - 16	24 - 25 May 84	Off feed
	15 - 18	24 - 27 May 84	Yellow stained nose, forepaws
	22 - 24	31 May - 2 Jun 84	Yellow stained nose, forepaws
	26 - 28	4 - 6 Jun 84	Yellow stained nose, forepaws

Individual Maternal Clinical Signs - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day (s)	Date(s)	Signs
84F255	26 26 - 28 28 29	21 May 84 21 - 23 May 84 23 May 84 24 May 84	Soft feces Yellow stained nose Alopecia, hindleg At cesarean section, gall bladder enlarged, soft; dark spots on ovaries
84F259	29	29 May 84	At cesarean section, pale areas on liver
84F263	29	7 Jun 84	At cesarean section, cysts on fallopian tubes and ovaries; cysts on spleen
84F267	6 - 8 8 - 9 12 14 18 20 - 23 24 - 25 27 29	9 - 11 May 84 11 - 12 May 84 15 May 84 17 May 84 21 May 84 23 - 26 May 84 27 - 28 May 84 30 May 84 1 Jun 84	Diarrhea Yellow stained nose Off feed Yellow stained nose Off feed Off feed Yellow stained nose, forepaws Off feed At cesarean section, dark spots on ovaries.

Individual Maternal Clinical Signs - 200 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day(s)	Date(s)	Signs
84F250	0 - 1	11 - 12 Jun 84	Yellow dried mucus around eyes; brown stain perianal; yellow stained nose, forepaws.
	9 - 11	20 - 22 Jun 84	Off feed
	14 - 18	25 - 29 Jun 84	Off feed
	20 - 22	1 - 3 Jul 84	Off feed
	28	9 Jul 84	Off feed
	29	10 Jul 84	At cesarean section, dark spots on ovary
84F254	5 - 9	25 - 29 Jun 84	Off feed
	12 - 13	2 - 3 Jul 84	Off feed
	14	4 Jul 84	When grasped by nap of neck for dosing, rabbit produced a cry, tonic convulsions for approximately 30 seconds, then tremors for approximately 2 minutes, depressed corneal reflex during convulsions and tremors; then appeared to be normal.
			Rabbit was returned to cage for 10 minutes; then was dosed.
	19 - 22	9 - 12 Jul 84	Off feed
	20	10 Jul 84	Yellow stained nose
	22	12 Jul 84	Diarrhea
	22 - 26	12 - 16 Jul 84	Soft feces
	26 - 28	16 - 19 Jul 84	Off feed
	29	19 Jul 84	At cesarean section, dark spots on ovaries; cysts on ovaries; lungs pale with dark red spots.

Individual Maternal Clinical Signs - 225 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day(s)	Date(s)	Signs
84F256	3	28 Jun 84	Off feed
	7	2 Jul 84	Off feed
	14 - 17	9 - 12 Jul 84	Off feed
	18 - 22	13 - 17 Jul 84	Soft feces
	21 - 25	16 - 20 Jul 84	Off feed
	22	17 Jul 84	Rabbit pulling out hair to make nest
	29	24 Jul 84	At cesarean section, mammary development;
			uterus enlarged and vascular as in
			pregnancy; cysts on fallopian tubes;
			uterus had 4 areas which appeared to
			be attachment sites for fetuses; dark
			spots on ovaries; fluid in vagina;
			corpora lutea, small, hard, red.

Individual Maternal Clinical Signs - 300 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day(s)	Date(s)	Signs
84F119	14	17 May 84	Off feed
	18	21 May 84	Off feed
	20 - 21	23 - 24 May 84	Off feed
	29	1 Jun 84	At cesarean section, ovaries small, dark spots
84F149	6	30 Apr 84	Off feed
	8 - 10	2 - 4 May 84	Off feed
	10	4 May 84	Yellow stained mouth
	14 - 16	8 - 10 May 84	Off feed
	15	9 May 84	Salivation
	16 - 22	10 - 16 May 84	Pallor lips, gums
	20 - 28	14 - 22 May 84	Off feed
	24	18 May 84	Nasal discharge, clear
	27 - 28	21 - 22 May 84	Nasal discharge, clear
	29	23 May 84	At cesarean section, dark spots on ovaries
84F112	8 - 25	8 - 25 May 84	Off feed
	27	27 May 84	Soft feces
	29	29 May 84	At cesarean section, dark spots on ovaries
84F163	1 - 9	19 - 18 May 84	Off feed
	12 - 17	21 - 26 May 84	Off feed
	15	24 May 84	Yellow stained perineal
	18 - 23	28 May - 1 Jun 84	Off feed
	20	29 May 84	Pallor lips, nose
	29	7 Jun 84	At cesarean section, dark spots on ovaries; cysts on fallopian tubes

Individual Maternal Clinical Signs - 450 mg/kg/day Hydroxyurea Animals

Maternal ID	Study Day(s)	Date(s)	Signs
84F242*	13 - 18	14 - 19 May 84	Off feed
	15	16 May 84	Inactive; salivation
	16	17 May 84	Dosing discontinued due to weight loss
	20 - 21	21 - 22 May 84	Rabbit pulling out hair to make nest
	21	22 May 84	Hypertonica
	24	25 May 84	Alopecia, head
84F247	26 - 29	27 - 30 May 84	Alopecia, head, paws
	29	30 May 84	At cesarean section, dark spots on ovaries; liver torsion
	8	2 May 84	Off feed
	14	8 May 84	Off feed
84F248*	14 - 15	5 - 9 May 84	Salivation
	15	9 May 84	Inactive; diarrhea
	16	9 May 84	Death
	11	12 May 84	Yellow stained mouth
84F249*	13 - 18	14 - 19 May 84	Off feed
	20 - 24	21 - 25 May 84	Off feed
	29	30 May 84	At sacrifice, dark spots on ovaries

*Treated with 450 mg/kg/day Hydroxyurea from Days 6 through 10, then 300 mg/kg/day from Days 11 through 18.

Individual Gestational Data - Control Animals

Maternal ID	Corpora Lutea	Implants	Implants* %	Resorptions	Resorptionst %	Number of Fetuses			
						Dead	Deads	Live	% Live«
84F238	11	10	91	0	0	1	10	9	90
84F246	10	9	90	0	0	0	0	9	100
84F251	8	5	62	1	20	0	0	4	80
84F258	11	8	73	0	0	0	0	8	100
84F260	13	13	100	0	0	0	0	13	100

*[implantations per litter/corpora lutea per litter] x 100

†[resorptions per litter/implantations per litter] x 100

«[dead fetuses per litter/implantations per litter] x 100

«[live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 25 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants [*]	Resorptions	Resorptions [‡]	Dead	Dead [§]	Live	Live [¶]	Number of Fetuses	
										Dead	Live
84F206	14	12	86	1	4	0	0	11	92		

*[(implantations per litter/corpora lutea per litter] x 100
 †[(resorptions per litter/implantations per litter] x 100
 ‡[dead fetuses per litter/implantations per litter] x 100
 §[(live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 50 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants*	% Resorptions		% Resorptionst		Dead		% Dead		Live		% Live	
				Resorptions		Resorptionst		Dead		% Dead		Live		% Live	
84F244	10	9	90	1	11	0	0	0	0	0	0	8	89		
84F253	11	9	82	0	0	0	0	0	0	0	0	9	100		
84F261	11	11	100	0	0	2	18	9	82						

*[implantations per litter/corpora lutea per litter] x 100

*[resorptions per litter/implantations per litter] x 100

*[dead fetuses per litter/implantations per litter] x 100

*[live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Number of Fetuses					
		Implants	Implants*	Resorptions	Resorptionst	Dead	Live
84F255	13	11	85	1	9	0	10
84F259	14	13	93	1	8	2	10
84F263	11	3	82	0	0	0	9
84F267	11	8	73	1	13	1	6

*[(implantations per litter/corpora lutea per litter] x 100

†[(resorptions per litter/implantations per litter] x 100

§[dead fetuses per litter/implantations per litter] x 100

«[live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 200 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants*	Resorptions	Resorption†	Number of Fetuses			
						Dead	Dead§	Live	% Live«
84F250	11	9	82	1	11	0	0	8	89
84F254	10	9	90	0	0	2	22	7	78

*[(implantations per litter/corpora lutea per litter] x 100

†[(resorptions per litter/implantations per litter] x 100

§[dead fetuses per litter/implantations per litter] x 100

«[live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 225 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants*	Resorptions	Resorptionst	Number of Fetuses			
						Dead	Dead\$	Live	Live«
84F256	10	4	40	4	100	0	0	0	0

*implantations per litter/corpora lutea per litter] x 100
 †resorptions per litter/implantations per litter] x 100
 \$dead fetuses per litter/implantations per litter] x 100
 «live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 300 mg/kg/day Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants*	Resorptions	Resorption†	Number of Fetuses		
						Dead	Dead‡	Live Live«
84F239	9	5	56	5	100	0	0	0
84F248	12	10	83	10	100	0	0	0
84F262	12	5	42	5	100	0	0	0
84F269	16	10	62	10	100	0	0	0

*[implantations per litter/corpora lutea per litter] x 100

†[resorptions per litter/implantations per litter] x 100

‡[dead fetuses per litter/implantations per litter] x 100

«[live fetuses per litter/implantations per litter] x 100

Individual Gestational Data - 450 mg/kg/day = Hydroxyurea Animals

Maternal ID	Corpora Lutea	Implants	Implants*	Resorptions	Resorptions†	Number of Fetuses			
						Dead	Dead‡	Live	Live«
84F242	18	12	67	12	100	0	0	0	0
84F257	12	8	60	8	100	0	0	0	0

*[implantations per litter/corpora lutea per litter] x 100
†[resorptions per litter/implantations per litter] x 100
‡[dead fetuses per litter/implantations per litter] x 100
«[live fetuses per litter/implantations per litter] x 100

Fetal Sex, Weight, and Length - Control Animals

Maternal ID	Sex		Mean Weight (g) \pm S.D.			Mean Length (mm) \pm S.D.		
	Male	Female	Male (%)	Fetal	Male	Female	Fetal	Male
84F238	6	3	67	34 \pm 5	36 \pm 4	31 \pm 5	93 \pm 4	93 \pm 4
84F246	4	5	44	43 \pm 5	43 \pm 2	43 \pm 7	100 \pm 5	99 \pm 3
84F251	1	3	25	46 \pm 2	44	46 \pm 2	95 \pm 7	99
84F258	5	3	63	40 \pm 5	40 \pm 5	41 \pm 6	98 \pm 3	98 \pm 3
84F260	11	2	85	31 \pm 5	31 \pm 4	31 \pm 10	86 \pm 5	86 \pm 5

Fetal Sex, Weight, and Length - 25 mg/kg/day Hydroxyurea Animals

Maternal ID	Sex		Mean Weight (g) \pm S.D.			Mean Length (mm) \pm S.D.				
	Male	Female	Male (%)		Fetal	Male	Female	Fetal	Male	Female
84F2.6	6	5		55	35 \pm 4	35 \pm 4	35 \pm 4	93 \pm 3	93 \pm 2	33 \pm 4

Fetal Sex, Weight, and Length - 50 mg/kg/day Hydroxyurea Animals

Maternal ID	Sex		Mean Weight (g) \pm S.D.			Mean Length (mm) \pm S.D.		
	Male	Female	Male (%)	Fetal		Fetal		Female
				Fetal	Male	Fetal	Male	
84F244	2	6	25	44 \pm 3	45 \pm 3	100 \pm 4	102 \pm 4	99 \pm 4
84F253	2	7	22	43 \pm 6	41 \pm 11	98 \pm 5	94 \pm 9	99 \pm 3
84F261	5	4	56	36 \pm 4	35 \pm 4	94 \pm 5	95 \pm 3	92 \pm 6

Fetal Sex, Weight, and Length - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	Sex		Mean Weight (g) \pm S.D.			Mean Length (mm) \pm S.D.		
	Male	Female	Male (%)	Fetal	Male	Female	Male	Female
84F255	5	5	50	37 \pm 5	39 \pm 4	35 \pm 5	91 \pm 6	91 \pm 7
84F259	7	3	70	31 \pm 5	31 \pm 5	31 \pm 2	89 \pm 6	89 \pm 1
84F260	3	6	33	38 \pm 3	36 \pm 2	39 \pm 3	94 \pm 4	93 \pm 3
84F261	2	4	33	42 \pm 3	39 \pm 2	43 \pm 3	101 \pm 3	102 \pm 4

Fetal Sex, Weight, and Length - 200 mg/kg/day Hydroxyurea Animals

Maternal ID	Sex		Mean Weight (g) \pm S.D.			Mean Length (mm) \pm S.D.		
	Male	Female	Male (%)	Fetal	Male	Female	Fetal	Male
84F250	5	3	62	35 \pm 4	35 \pm 4	35 \pm 4	93 \pm 4	94 \pm 4
84F254	4	3	57	34 \pm 4	33 \pm 6	35 \pm 2	91 \pm 4	89 \pm 4
								94 \pm 3

Fetal External Examination - Control Animals

Maternal ID	Variants		Malformations	
	No.*	No.† No. and Description of Each Variant	No.‡	No. and Description of Each Malformation
84F213	9	0	0	
84F247	9	0	0	
84F251	4	0	0	
84F273	8	0	0	
84F291	13	0	0	

*Number of fetuses examined.
†Number of fetuses with variants.
‡Number of fetuses with malformations.

Fetal External Examination - 25 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No. and Description of Each Variant	No.\$	No. and Description of Each Malformation
34E256	11	0	0	

*Number of fetuses examined

\$Number of fetuses with variants.

#Number of fetuses with malformations.

Fetal External Examination - 50 mg/kg/day Hydroxyurea Animals

Maternal ID	Variants			Malformations	
	No.*	No.†	No. and Description of Each Variant	No.§	No. and Description of Each Malformation
84F244	8	0		0	
84F253	9	0		0	
84F261	9	0		0	

*Number of fetuses examined.

†Number of fetuses with variants.

§Number of fetuses with malformations.

Fetal External Examination - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	Variants			Malformations	
	No.*	No.†	No. and Description of Each Variant	No.‡	No. and Description of Each Malformation
84F255	10	0		0	
84F259	10	0		1	1 Hyperflexed forepaw
84F263	9	0		0	
84F267	6	0		0	

*Number of fetuses examined.

†Number of fetuses with variants.

‡Number of fetuses with malformations

Fetal External Examination - 200 mg/kg/day Hydroxyurea Animals

Variants				Malformations	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.§	No. and Description of Each Malformation
84F25C	8	1	1 Body dark red	2	2 Curly tail
84F254	7	0		1	1 Tongue malformed

*Number of fetuses examined.

†Number of fetuses with variants.

§Number of fetuses with malformations.

Fetal Visceral Examination - Control Animals

Maternal ID	No.*	No.†	Variants		Malformations	
			No. and Description of Each Variant	No.\$	No. and Description of Each Malformation	
84F238	4	0		0		
84F246	4	1	1 Nasal concha underdeveloped	0		
84F251	2	1	1 Cerebrum underdeveloped, right hemisphere	0		
84F258	4	0		0		
84F260	6	2	1 Lateral ventricle dilated 1 Kidney lobular	0		

*Number of fetuses examined.

†Number of fetuses with variants.

\$Number of fetuses with malformations.

Fetal Visceral Examination - 25 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No.+ of Each Variant	No. and Description of Each Variant	No.\$ No. and Description of Each Malformation
84F266	5	4	1 Lateral ventricle dilated 1 Arachnoid space dilated 1 Heart left ventricle slightly enlarged 1 Gall bladder small 1 Kidneys small	0

*Number of fetuses examined.

+Number of fetuses with variants.

\$Number of fetuses with malformations.

Fetal Visceral Examination - 50 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.‡ No. and Description of Each Malformation
84F244	4	1	1 Ovary short/thickened	0
84F253	4	1	1 Kidney lobular	2 1 Heart left atria underdeveloped, marked 1 Kidney ectopic
84F261	4	1	1 Lateral ventricles dilated	0

*Number of fetuses examined.

†Number of fetuses with variants.

‡Number of fetuses with malformations.

Fetal Visceral Examination - 150 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No.† No. and Description of Each Variant	No.‡ No. and Description of Each Malformation	
84F255	4	2 Nasal concha underdeveloped 1 Ovary short/thickened	1 1 Heart right atria underdeveloped, marked	
84F259	5	0	1 1 Esophagus <u>situs</u> <u>inversus</u>	
84F263	4	4 Nasal concha underdeveloped 1 Lateral ventricle dilated 1 Foramen magnum dilated 2 Gall bladder small 1 Renal pelvis dilated	0	
84F267	3	0	0	

*Number of fetuses examined.
†Number of fetuses with variants.
‡Number of fetuses with malformations.

Fetal Visceral Examination - 200 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.‡ No. and Description of Each Malformation
84F250	4	2	1 Nasal concha underdeveloped	1 1 Stomach situs inversus
			2 Heart atria small	
84F254	3	2	2 Nasal concha underdeveloped	1 1 Stomach situs inversus
			1 Renal pelvis dilated	

*Number of fetuses examined.

†Number of fetuses with variants.

‡Number of fetuses with malformations.

Fetal Skeletal Examination - Control Animals

Variants			Malformations	
Maternal ID	No. *	No. †	No. and Description of Each Variant	No. \$ No. and Description of Each Malformation
84F238	5	5	4 13 pairs of ribs 1 Unilateral rudimentary 13th rib 1 Scapula spine crooked	0
84F246	5	5	4 13 pairs of ribs 1 Short 13th rib 1 Unilateral rudimentary 13th rib	1 1 Rudimentary cervical rib
84F251	2	2	2 13 pairs of ribs 1 Short 13th rib	0
84F258	4	4	4 13 pairs of ribs	0
84F260	7	6	4 13 pairs of ribs 2 Unilateral rudimentary 13th rib 2 Sternebrae split/unilateral ossification 1 Short 13th rib	0

*Number of fetuses examined.
†Number of fetuses with variants.
\$Number of fetuses with malformations.

Petal Skeletal Examination - 25 mg/kg/day Hydroxyurea Animals

		Variants		Malformations	
Maternal ID	No.*	No.†	No. and Description of Each Variant	No.\$	No. and Description of Each Malformation
64E168	6	5	5 13 pairs of ribs 1 Short 16th rib	0	

*Number of fetuses examined.
 †Number of fetuses with variants.
 \$Number of fetuses with malformations.

Fetal Skeletal Examination - 50 mg/kg/day Hydroxyurea Animals

Variants			Malformations	
Maternal ID	No.*	No.† No. and Description of Each Variant	No.\$	No. and Description of Each Malformation
84F244	4	4 13 pairs of ribs	0	
84F253	5	5 13 pairs of ribs	0	
84F261	5	5 13 pairs of ribs	0	

*Number of fetuses examined.
†Number of fetuses with variants.
\$Number of fetuses with malformations.

Patal Skeletal Examination - 150 mg/kg/day Hydroxyurea Animals

Variants			Malformations		
Material ID	No.*	No.†	No. and Description of Each Variant	No.‡	No. and Description of Each Malformation
84F255	6	6	1 13 pairs of ribs 1 Short 1st rib 1 Frontal/parietal suture jagged 2 Sternebrae split or unilateral ossification	3	3 20 Thoracic + lumbar vertebrae 1 Unilateral 14th rib
84F259	5	3	1 Scapula spine crooked 1 Sternebrae fused 2 Sternebrae scrambled 1 Sternebrae split or unilateral ossification	5	5 14 Pairs of ribs 4 20 Thoracic + lumbar vertebrae 1 21 Thoracic + lumbar vertebrae
84F263	5	5	1 12 pairs of ribs 1 Sternebrae fused 1 Sacral vertebral arch wide	5	5 8 Cervical vertebrae 3 20 Thoracic + lumbar vertebrae
84F267	3	1	1 Short 1st rib 1 Sternebrae split or unilateral ossification	3	3 14 Pairs of ribs 3 20 Thoracic + lumbar vertebrae

*Number of fetuses examined.
†Number of fetuses with variants
‡Number of fetuses with malformations

Summary of Hydronephroses Animals

Malformations

No. and Description of Each Variant	No. of Each Malformation	No. and Description of Each Malformation
13 pairs of ribs	4	3 rudimentary cervical rib
Horns of hyoid not ossified		4 8 Cervical vertebrae
Sternebrae scrambled		4 20 Thoracic + lumbar vertebrae
Sternebrae split or unilateral ossification		2 Coccygeal vertebral arch misaligned and fused
Pubis incomplete ossification		
Radius and ulna small		
13 Pairs of ribs	4	2 Rudimentary cervical rib
Sternebrae diagonal shape		1 Scoliosis
Cervical vertebral centrum split, malrotated		4 8 Cervical vertebrae
		1 20 Thoracic + lumbar vertebrae

Number of animals examined.

Number of animals with variants.

Number of animals with malformations.

Summary of Field Examination Findings - Control Animals

Material	Number Examined	Number with Variants	Visceral		Skeletal	
			Number Examined	Malformed Variants No.	Number Examined	Malformed Variants No.
140000	3	0	4	0	5	0
140001	3	0	4	0	5	1
140002	4	0	2	0	2	0
140003	3	0	4	0	4	0
140004	3	0	5	0	7	0
140005	3	0	5	0	6	0
140006	3	0	5	0	5	0
140007	3	0	4	0	5	0
140008	3	0	4	0	5	0
140009	3	0	4	0	5	0
140010	3	0	4	0	5	0
140011	3	0	4	0	5	0
140012	3	0	4	0	5	0
140013	3	0	4	0	5	0
140014	3	0	4	0	5	0
140015	3	0	4	0	5	0
140016	3	0	4	0	5	0
140017	3	0	4	0	5	0
140018	3	0	4	0	5	0
140019	3	0	4	0	5	0
140020	3	0	4	0	5	0
140021	3	0	4	0	5	0
140022	3	0	4	0	5	0
140023	3	0	4	0	5	0
140024	3	0	4	0	5	0
140025	3	0	4	0	5	0
140026	3	0	4	0	5	0
140027	3	0	4	0	5	0
140028	3	0	4	0	5	0
140029	3	0	4	0	5	0
140030	3	0	4	0	5	0
140031	3	0	4	0	5	0
140032	3	0	4	0	5	0
140033	3	0	4	0	5	0
140034	3	0	4	0	5	0
140035	3	0	4	0	5	0
140036	3	0	4	0	5	0
140037	3	0	4	0	5	0
140038	3	0	4	0	5	0
140039	3	0	4	0	5	0
140040	3	0	4	0	5	0
140041	3	0	4	0	5	0
140042	3	0	4	0	5	0
140043	3	0	4	0	5	0
140044	3	0	4	0	5	0
140045	3	0	4	0	5	0
140046	3	0	4	0	5	0
140047	3	0	4	0	5	0
140048	3	0	4	0	5	0
140049	3	0	4	0	5	0
140050	3	0	4	0	5	0
140051	3	0	4	0	5	0
140052	3	0	4	0	5	0
140053	3	0	4	0	5	0
140054	3	0	4	0	5	0
140055	3	0	4	0	5	0
140056	3	0	4	0	5	0
140057	3	0	4	0	5	0
140058	3	0	4	0	5	0
140059	3	0	4	0	5	0
140060	3	0	4	0	5	0
140061	3	0	4	0	5	0
140062	3	0	4	0	5	0
140063	3	0	4	0	5	0
140064	3	0	4	0	5	0
140065	3	0	4	0	5	0
140066	3	0	4	0	5	0
140067	3	0	4	0	5	0
140068	3	0	4	0	5	0
140069	3	0	4	0	5	0
140070	3	0	4	0	5	0
140071	3	0	4	0	5	0
140072	3	0	4	0	5	0
140073	3	0	4	0	5	0
140074	3	0	4	0	5	0
140075	3	0	4	0	5	0
140076	3	0	4	0	5	0
140077	3	0	4	0	5	0
140078	3	0	4	0	5	0
140079	3	0	4	0	5	0
140080	3	0	4	0	5	0
140081	3	0	4	0	5	0
140082	3	0	4	0	5	0
140083	3	0	4	0	5	0
140084	3	0	4	0	5	0
140085	3	0	4	0	5	0
140086	3	0	4	0	5	0
140087	3	0	4	0	5	0
140088	3	0	4	0	5	0
140089	3	0	4	0	5	0
140090	3	0	4	0	5	0
140091	3	0	4	0	5	0
140092	3	0	4	0	5	0
140093	3	0	4	0	5	0
140094	3	0	4	0	5	0
140095	3	0	4	0	5	0
140096	3	0	4	0	5	0
140097	3	0	4	0	5	0
140098	3	0	4	0	5	0
140099	3	0	4	0	5	0
140100	3	0	4	0	5	0

Table 1. Total Examination Findings - 75 mg/kg/day Hydroxyurea Animals

Animal ID	External				Visceral				Skeletal			
	Number Examined	Number	Malformed	Variant	Number Examined	Number	Malformed	Variant	Number Examined	Number	Malformed	Variant
	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8	No. 8
145266	1	0	0	0	1	0	0	0	6	0	0	8

REPORT

1. NAME _____
 2. ADDRESS _____
 3. CITY _____
 4. STATE _____
 5. ZIP _____
 6. PHONE _____
 7. DATE _____
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 99. NO. _____
 100. NO. _____

1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
3	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

Incidence of Fetal Examination Findings - 150 mg/kg/day Hydroxyurea Animals

Maternal ID	External				Visceral				Skeletal			
	Number Examined		Malformed Variants		Number Examined		Malformed Variants		Number Examined		Malformed Variants	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
84F255	10		0	0	4		1	25	2	50	3	50
84F259	10		0	0	5		1	20	0	0	5	100
84F263	3		0	0	4		0	0	4	100	5	100
84F267	6		0	0	3		0	0	0	0	3	100

6-11-1944
10-11-1944
12-11-1944
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18-11-1944
20-11-1944
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1-12-1944
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15-12-1944

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